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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

ZARA, JANE J

ART UNIT	PAPER NUMBER
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1635

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/669,162	Applicant(s) BREAKER ET AL.	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 December 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 20, 21 and 46-83 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-7, 20, 21, 46-83 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4-27-09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office action is in response to the communication filed 12-11-08.

Claims 1-7, 20, 21, 46-83 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 20, 21, 46-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to regulatable gene expression constructs comprising a nucleic acid molecule encoding RNA comprising a riboswitch operably linked to a sequence, wherein the riboswitch regulates expression of the sequence, wherein the riboswitch comprises any aptamer domain and any expression platform domain, which

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domains are optionally heterologous, and which riboswitch is optionally a non-natural derivative of a naturally-occurring riboswitch.

The specification teaches the 5'-UTR of the *B. subtilis* xpt-pbuX mRNA as a potential guanine-specific riboswitch (figures 24-26 of the instant specification). The specification also teaches a comparison between this 5'-UTR fragment (of 185 nucleotides) and other bacterial sequences, whereby a conserved RNA motif, termed a "G box" has been identified as domain for a guanine-riboswitch, suggesting that conserved secondary and tertiary structures are likely a pre-requisite for adopting the required, yet undefined three-dimensional fold necessary for riboswitch function (see e.g. p. 139 of the instant specification). The specification also discusses the ability of hypoxanthine, xanthine and adenine to also effect target nucleic acid cleavage under various conditions with this 5'-UTR fragment. In addition, the specification teaches various examples of riboswitches comprising aptamers and expression platforms, including btuB mRNA and Ado cbl, TPP and related analogs linked to Thi M or Thi C RNA, Sam-responsive ribozyme also comprising Yit J mRNA, alignments of eukaryotic domains with bacterial TPP-dependent riboswitches, models for various aptamers, including coenzyme B12, TPP, FMN, SAM, guanine, adenine, and lysine aptamer consensus motifs. The specification also teaches adenine aptamers and ydhI RNA, FMN aptamers and *B. subtilis* rib D, consensus lysine (L box) of Lys C of 5' UTR of *B. subtilis* and various L box motifs based on prokaryotic and archael organisms sequences, G box consensus motifs from bacteria adjacent to Xpt-pbux mRNA of *B. subtilis*.

These consensus sequences and adjacent regulatable RNA sequences, however, are not representative of the ability to mix and match any aptamer with any regulatable sequence for producing the broad genus of riboswitches claimed, which provide for controlling regulation of an operably linked sequence. The disclosed species are particular consensus sequences that are compatible with a particular adjacent regulatable sequence, often first identified in a particular bacterial mRNA sequence as being adjacent to that regulatable sequence. It is therefore unclear, from the combined teachings in the instant disclosure, which of the aptamers in the riboswitch are capable of being mixed and matched with which regulatable sequences comprising the expression platform, and the claims read broadly on the ability to mix and match any aptamer with any regulatable sequence to produce any riboswitch.

Applicant's arguments filed 5-13-08 have been fully considered but they are not persuasive. Applicant argues that adequate written description has provided for the genus of nucleic acid molecules claimed because the specification provides numerous examples of structural features and sequence relationships of riboswitches, and provides description of the key structural features and sequence relationships necessary for the operation of riboswitches in general. Applicant also argues that the consensus sequences provided clearly demonstrate possession of the broad general subject matter of the present claims. Applicant additionally argues that consensus elements of other guanine aptamers in guanine responsive riboswitches have been provided and that one of skill in the art would have been able to readily produce functional riboswitches and the riboswitch can comprise any aptamer. In addition,

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Applicant has provided various post-filing publications providing higher-order structural details and descriptions of riboswitches that validate findings and predictions originally disclosed in the instant specification. The generic structural descriptions of the expansive genus of riboswitches, however, provide for a means for screening for other riboswitches, but do not substitute for what was in possession at the time of filing.

The very broad genus of molecules claimed, comprising regulatable gene expression constructs comprising riboswitches that are activated by a trigger molecule and produce a signal upon activation, and which constructs further comprise any control strand, any aptamer domain, and linked to any expression platform domain comprising a regulated strand, has not been adequately described. This very broad genus encompasses a vast array of molecules and combination of subunits or component parts, and the disclosure fails to provide a representative number of species for the very broad genus which provide for the concise combinations of any aptamers in combination with any expression platforms as claimed, whereby the combinations provide for riboswitches capable of regulating expression of an operably linked sequence, or which riboswitches produce a signal upon activation by a trigger molecule.

The examples given, and the generic descriptions of riboswitches, comprising an aptamer domain and an expression platform, the generic descriptions of structure function relationships for some identified (and proposed) stem structures of platform domains, and the sequence comparisons between previously described riboswitches found in nature, and sequence data bases, together do not provide the concise structural features required for the very broad genus of compounds claimed. Applicant

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asserts that those of skill in the art would have been able to readily produce functional riboswitches using what is known in the art. But to satisfy written description requirements, Applicant must be in possession at the time of filing of an adequate representation of species for the broad genus of compounds claimed, and not merely have the ability to screen for such species. The ability to screen does not replace the need for possession at the time of filing.

For these reasons, the instant disclosure does not provide adequate description for the expansive genus of compounds claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 20, 21, 46-58, 70-83 are rejected under 35 U.S.C. 102(a) as being anticipated by Nahvi et al (Chem. & Biology, Vol. 9, pages 1043-1049, published online 9-19-2002).

Nahvi et al (Chem. & Biology, Vol. 9, pages 1043-1049, published online 9-19-2002) teach a gene expression construct comprising a riboswitch which is derived from either a naturally occurring or conservative base sequences thereof, or from a non-

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naturally occurring riboswitch, and is operably linked to a coding region which is optionally an expression construct or recombinant polypeptide, which riboswitch comprises an aptamer domain and an expression platform domain, which aptamer domain comprises a P1 stem, which P1 stem comprises an aptamer strand and a heterologous control strand, and the expression platform comprises regulatory element which is optionally a transcription initiation site and comprises a regulated strand, and which regulated or control strand forms a stem structure, and which riboswitch is a derived from an adenosylcobalamin-responsive riboswitch (see entire document, esp. figure 1 on p. 1044, figure 1 on p. 1045, figure 4 on p. 1046, figure 5 on p. 1047 and text on pages 1047-8).

Claims 1, 2, 4, 5, 7, 20, 21, 46, 70-83 are rejected under 35 U.S.C. 102(b) as being anticipated by Werstuck et al (Science, Vol. 282, pages 296-298, 1998).

Werstuck et al (Science, Vol. 282, pages 296-298, 1998) teach regulatable gene expression constructs comprising a nucleic acid molecule encoding an RNA comprising a riboswitch operably linked to a sequence encoding a protein, wherein the riboswitch regulates expression of the protein, wherein the riboswitch regulates transcription or translation of the sequence, which riboswitch comprises an aptamer domain and an expression platform domain, which riboswitch is optionally derived from a natural or a non-natural derivative, and which aptamer domain and expression platform domain are heterologous (See entire document, esp. Fig. 1 and 3).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Jane Zara

5-18-09

/Jane Zara/

Primary Examiner, Art Unit 1635